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Original Article

Improved survival with induction chemotherapy and conversion surgery in locally advanced unresectable pancreatic cancer: a single institution experience

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Abstract: Both efficacy and tolerability are critical issues in choosing neoadjuvant chemotherapy in patients with unresectable locally advanced pancreatic cancer (LAPC). The optimal regimen and the impact of conversion surgery on patient survival remains insufficiently reported in Asain population. Therefore, we conducted a retrospective study aiming to evaluate the resection rate after different induction chemotherapy regimen and its impact toward survival. All patients with pancreatic cancer treated in our institute from 2013 to 2020, a total of 730 patients, were reviewed and 131 patients with LAPC were identified. For cohort homogeneity, 14 patients receiving induction concurrent chemoradiotherapy initially were excluded and 117 patients receiving induction chemotherapy were included in the study. Most patients (90 of 117, 77%) received triplet induction chemotherapy, including the combination of S1, leucovorin, oxaliplatin and gemcitabine (SLOG) in 48, modified FOLFIRINOX in 21 and the combination of gemcitabine, oxaliplatin, fluorouracil and leucovorin (GOFL) in 21. The tumor response rate (19%-33%), the surgical exploration rate (38%-52%) and the mOS (15.4-23.0 months) were not significantly different among the three triplets. Both GOFL and SLOG regimen had comparable efficacy and less neutropenia as compared to mFOLFIRINOX. Conversion surgery was performed in 34 of 117 (29%) patients after induction chemotherapy. The median overall survival (mOS) in patients with and without conversion surgery were 29.1 and 14.1 months, respectively (P<0.0001). Radiological response alone was not a reliable indicator of successful conversion surgery. Patients who underwent conversion surgery had significantly better survival and thus highlighted the importance of surgical exploration in all patients who did not have progressive disease after induction chemotherapy.

Keywords: Locally advanced pancreatic cancer, combination induction chemotherapy, conversion surgery

Introduction

Pancreatic ductal adenocarcinoma (PDAC), characterized by its poor prognosis, is the third or fourth leading cause of cancer-related death in most of developed countries and is projected to be the second leading cause of cancer-related death by 2026 in the U.S. [1, 2]. The main driver for poor survival has been largely attributed to the advanced stage upon diagnosis with less than 20 percent of patients suitable for curative resection. Approximately 30% of

patients presented with unresectable locally advanced PDAC (LAPC) characterized by the involvement of major vessels [3, 4]. As the improvement of image resolution, and the known differences in their clinical outcomes after surgical intervention, stage III PDAC has been further divided into borderline resectable pancreatic cancer (BRPC) and unresectable locally advanced pancreatic cancer (LAPC) according to whether the tumor involved major vessel greater than 180° or not [5].

Systemic chemotherapy has been the main treatment strategy for patients of both LAPC and metastatic pancreatic cancer (mPC) in the era of gemcitabine monotherapy, as evident by the inclusion of both patients with either locally advanced disease or metastatic diseases in earlier phase III trials evaluating gemcitabine *versus* gemcitabine-based doublet for advanced pancreatic cancer. The median overall survival (mOS) of patients in gemcitabine monotherapy arm was 8.8-13 months for LAPC [6, 7]. The data was largely confirmed by the LAP-07 trial in which patients received gemcitabine monotherapy after first randomization was 13.8 months [8]. On the other hand, the pivotal trials that demonstrated the survival benefits of modern chemotherapy regimens, FOLFIRINOX and nab-paclitaxel plus gemcitabine (nab-P+Gem), only included patients with mPC. The first publication that indicated the usefulness of FLOFIRINOX for patients with LAPC was a retrospective, pooled analysis. Of the 315 patients with survival outcomes, the medain progression-free survival (mPFS) and mOS were 15.0 (95% confidence interval [95% CI], 13.7-16.3) months and 24.2 (95% CI, 21.7-26.8) months, respectively. Among them, 59 could undergo R0 conversion resection. Subsequently, several large-scale, retrospective, single institutional or multi-center studies showed the survival benefit of conversion surgery for LAPC after induction chemotherapy, mostly with FOLFIRINOX [9]. Currently, FOLFIRINOX is the recommended frontline therapy for fit LAPC patients by the guidelines of the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the Japanese Pancreas Society (JPS) [10-12].

Both efficacy (increase resectibility) and tolerability (no delay of surgey) are critical issues in neoadjuvant setting. Although FOLFIRINOX is effective, treatment related toxicities might preclude its continuation treatment. In a retrospective study in BRPC/LAPC, 27 of 139 (19.4%) patients required neoadjuvant chemotherapy switch due to toxicity or intolerance. For known being more toxic in Asian population [13], and late and limited reimbursement of both FOLFIRINOX and nab-P+Gem regimens for patients with metastatic diseases in Taiwan, our practice for LAPC has been largely relied on our own gemcitabine-based triplet chemotherapy regimens consisting of biweekly gemctiabine, oxaliplatin plus leucovorin modulated fluoropyrimidine, either 48 hour infusion of 5-FU/LV (the GOFL regimen) or oral S-1/LV (the SLOG regimen). Both regimens were effective (objective response rate [ORR] 33.3-40.7%) and well-tolerated (24.4-40% of grade 3-4 neutropenia) in phase II studies [14-17].

The impact of conversion surgery on patient survival remains insufficiently reported in Asian population. Besides, it remains unclear (1) which is the preferable regimen in terms of resection rate, survival and safety profile; (2) whether a more aggressive surgery strategy is beneficial (eg, surgical exploration in those without radiological response). Herein, we report a retrospective study of LAPC patients receiving different frontline induction chemotherapy to explore the resection rate after different regimen and its impact toward survival for patients with LAPC.

Materials and methods

All patients with PDAC receiving treatment at National Cheng Kung University Hospital (NCKUH) from 2013 to 2020 were identified by institutional PDAC tumor board registration. The inclusion criteria was patients with LAPC. The exclusion criteria included (1) patients with LAPC who did not receive chemotherapy as initial treatment (2) patients with BRPC. All identified cases were manually reviewed for clinical stage, treatment course and baseline Eastern Cooperative Oncology Group performance status (ECOG PS), albumin and CA 19-9 at baseline and before surgical exploration. The initial radiological image before treatment was also reviewed for tumor size and vessel encasement status to determine whether the case was classified as BRPC or LAPC. The definition of BRPC was based on the anatomical criteria from the international consensus of International Association of Pancreatology [18]. BRPC

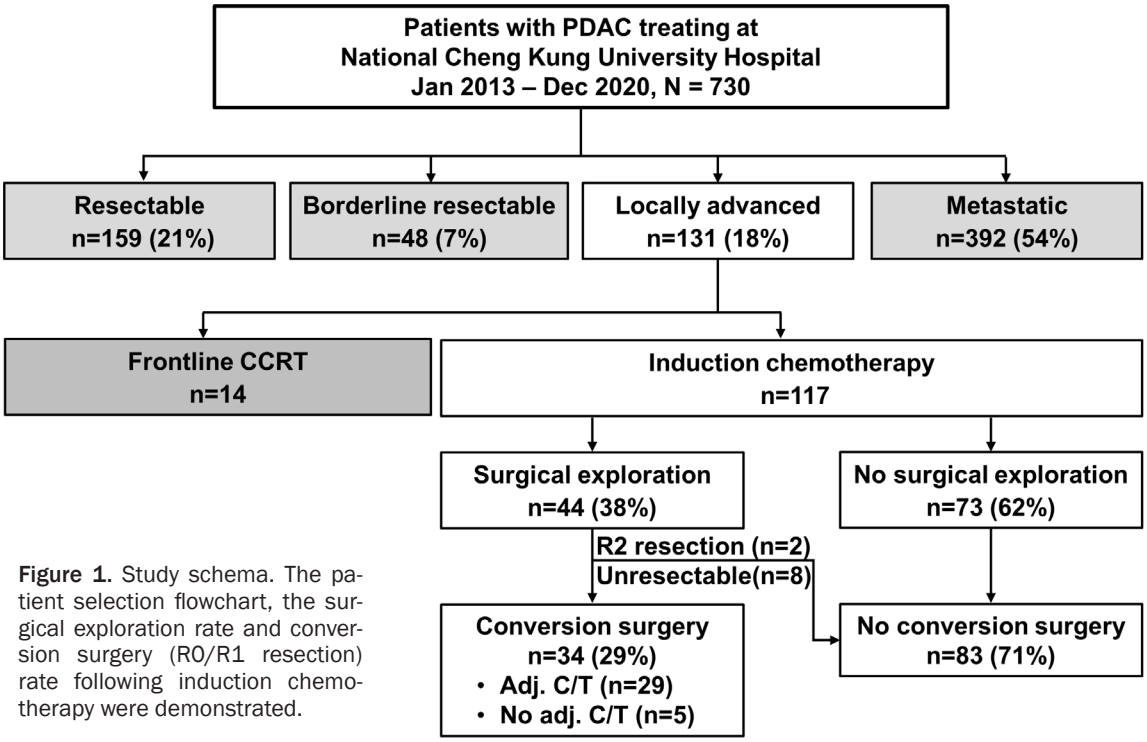

Figure 1. Study schema. The patient selection flowchart, the surgical exploration rate and conversion surgery (R0/R1 resection) rate following induction chemotherapy were demonstrated.

was defined as a tumor contact of less than 180° of celiac trunk/superior mesenteric artery without deformity or stenosis, or tumor contact 180° or greater or bilateral narrowing of portal vein/superior mesenteric vein without contact of artery.

Tumor assessment was done by computed tomography (CT) or magnetic resonance imaging (MRI) before treatment and every 12 weeks after treatment mainly based on national health insurance regulation and at physician's discretion. Tumor response was assessed by The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events were retrospectively reviewed based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3. This retrospective study was approved by Institutional Review Board (approval number NCKUH A-ER-108-113) with waiver of informed consents and followed the Declaration of Helsinki.

Descriptive statistics are presented as median or percentage, as appropriate. Kolmogorov-Smirnov test is used for evaluation of normality of data distribution. Fisher's exact test was used to compare the difference in proportion between groups. The median duration of follow-up was estimated using the reverse Kaplan-Meier method. Progression-free survival (PFS) was calculated from the initial treatment to documented radiological/clinical progression, recurrence in patients who underwent conversion surgery or death. PFS was censored at discontinuation of a regimen without progression (eg, intolerance or patient choice), loss of follow-up or data cut-off. Overall survival was calculated from the initial treatment to death while censoring for loss of follow-up or data cut-off. Survival was estimated by the Kaplan-Meier method, and survival differences between groups were compared by the log-rank test. All variables with $P<0.05$ were statistically significant. All statistical analyses were performed using R version 4.0.5 (R Core Team, Vienna, Austria).

Results

Patient cohort

A total of 730 patients with PDAC were identified and 179 patients (25%) were classified as stage III PDAC. For cohort homogeneity, 48 patients with BRPC and 14 patients with LAPC treated with induction concurrent chemoradiotherapy (CCRT) were excluded. Finally, 117 patients with LAPC treated with induction chemotherapy were included in the study (**Figure 1**).

Table 1. Baseline characteristics

	Overall (N=117)	First line chemotherapy				Conversion surgery	
		SLOG (N=48)	mFOLFIRINOX (N=21)	GOFL (N=21)	Others (N=27)	Yes (N=34)	No (N=83)
Age							
<55 years old	25 (21.4%)	11 (22.9%)	3 (14.3%)	7 (33.3%)	4 (14.8%)	8 (23.5%)	17 (20.5%)
55-70 years old	69 (59.0%)	28 (58.3%)	18 (85.7%)	12 (57.1%)	11 (40.7%)	20 (58.8%)	49 (59.0%)
>70 years old	23 (19.7%)	9 (18.8%)	0 (0%)	2 (9.5%)	12 (44.4%)	6 (17.6%)	17 (20.5%)
Gender							
Female	49 (41.9%)	21 (43.8%)	4 (19.0%)	10 (47.6%)	14 (51.9%)	15 (44.1%)	34 (41.0%)
Male	68 (58.1%)	27 (56.3%)	17 (81.0%)	11 (52.4%)	13 (48.1%)	19 (55.9%)	49 (59.0%)
Tumor location							
Head	46 (39.3%)	20 (41.7%)	5 (23.8%)	7 (33.3%)	14 (51.9%)	17 (50.0%)	29 (34.9%)
Body	43 (36.8%)	18 (37.5%)	12 (57.1%)	6 (28.6%)	7 (25.9%)	8 (23.5%)	35 (42.2%)
Tail	10 (8.5%)	4 (8.3%)	0 (0%)	3 (14.3%)	3 (11.1%)	4 (11.8%)	6 (7.2%)
Overlap including head	11 (9.4%)	4 (8.3%)	2 (9.5%)	2 (9.5%)	3 (11.1%)	2 (5.9%)	9 (10.8%)
Overlap excluding head	7 (6.0%)	2 (4.2%)	2 (9.5%)	3 (14.3%)	0 (0%)	3 (8.8%)	4 (4.8%)
BMI, Median (IQR)	22.9 (20.1-25.1)	23.3 (21.6-24.6)	22.9 (19.7-25.9)	22.2 (20.7-23.7)	22.3 (19.6-24.8)	23.3 (21.4-25.6)	22.6 (19.7-24.9)
ECOG							
0-1	108 (92.3%)	45 (93.8%)	20 (95.2%)	21 (100%)	22 (81.5%)	34 (100%)	74 (89.2%)
2	9 (7.7%)	3 (6.3%)	1 (4.8%)	0 (0%)	5 (18.5%)	0 (0%)	9 (10.8%)
Baseline albumin, g/dl							
Median (IQR)	4.00 (3.70-4.40)	3.90 (3.60-4.20)	4.35 (4.03-4.50)	4.30 (3.88-4.60)	3.95 (3.53-4.35)	4.00 (3.70-4.33)	4.10 (3.60-4.40)
Not checked	14 (12.0%)	5 (10.4%)	3 (14.3%)	1 (4.8%)	5 (18.5%)	6 (17.6%)	8 (9.6%)
Baseline CA-19.9, U/mL							
Median (IQR)	355 (59.0-1340)	282 (53.7-708)	478 (37.7-699)	526 (108-2530)	655 (68.7-1420)	282 (77.9-1570)	369 (49.2-1070)
Not checked	7 (6.0%)	2 (4.2%)	0 (0%)	0 (0%)	5 (18.5%)	2 (5.9%)	5 (6.0%)
Tumor size, cm, median (IQR)	4.10 (3.20-5.00)	3.85 (3.00-4.58)	4.50 (3.70-5.50)	4.20 (3.60-5.10)	3.80 (3.25-4.40)	3.90 (3.00-4.45)	4.10 (3.25-5.00)

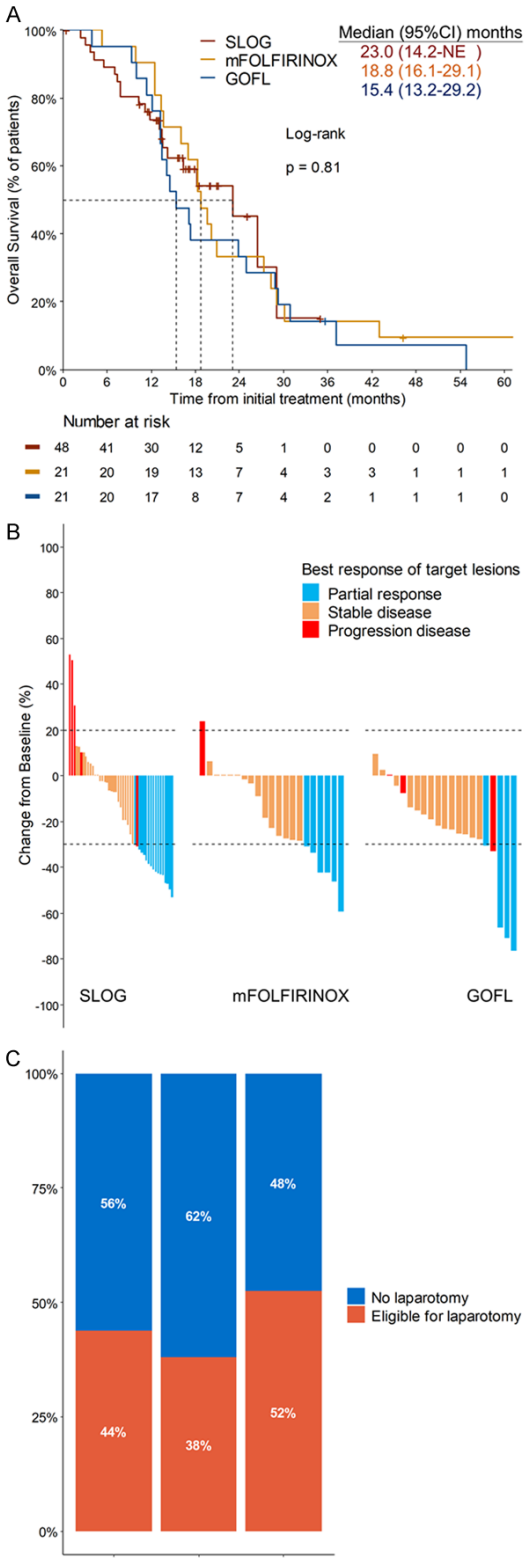

Figure 2. Treatment efficacy of commonly used chemotherapy regimen. A. Overall survival of three commonly used triplet chemotherapy SLOG, mFOLFIRINOX and GOFL. B. Best tumor response of each triplet. C. Surgical exploration rate of each triplet.

Induction chemotherapy regimen

Only 9 patients (7.7%) received gemcitabine or S1 monotherapy while the other 108 patients received a variety of different combination; the majority of patients received triplet chemotherapy, including combination of S1, leucovorin, oxaliplatin and gemcitabine (SLOG) in 48 patients, modified FOLFIRINOX (mFOLFIRINOX, reducing irinotecan to 150 mg/m^2 and omitting bolus 5-FU) in 21 patients and combination of gemcitabine, oxaliplatin, fluorouracil and leucovorin (GOFL) in 21 patients (**Table 1**). The remainder underwent different kinds of regimen with each regimen no more than 10 patients and were not suitable for detailed analysis. The baseline characterictics were not significantly different among patients received three major triplet except there were 19% of patients in SLOG arm were more than 70 years old while all patients in mFOLFIRINOX arm were aged under 70 (**Table 1**).

As of data cut-off on December 31th, 2021, the median duration of follow-up was 35.0 months (95% confidence interval [95% CI], 20.9-46.3). The mOS were not significantly different among 3 commonly used triplet, 23.0 months (95% CI, 14.2-NE) in SLOG, 18.8 months (95% CI, 16.1-29.1) in mFOLFIRINOX and 15.4 months (95% CI, 13.2-29.2) in GOFL (**Figure 2A**). The ORR of each triplet chemotherapy SLOG, mFOLFIRINOX and GOFL were 33.3%, 28.6% and 19.0%, respectively (**Figure 2B**). The surgical exploration rate after induction chemotherapy of SLOG, mFOLFIRINOX and GOFL were 21/48 (44%), 8/21 (38%) and 11/21 (52%), respectively (**Figure 2C**).

Impact of conversion surgery on survival

Conversion surgery (R0/R1 resection) was performed in 34 of 117 (29%) patients following induction chemotherapy. The baseline characteristics, including age (62.5 vs. 65 years), porpotion of ECOG PS 0-1 (100% vs. 89.2%), albumin (4.0 vs. 4.1 g/dl), CA-19.9 (282 vs. 369 U/mL) and tumor size (3.9 vs. 4.1 cm), were not significnatly different between patients underwent conversion surgery or not (**Table 1**). Among 117 patients, 30 patients (25.6%) had partial response and 15 of them underwent conversion surgery; 69 patients had stable disease and 18 of them underwent conversion surgery (**Table 2**). Three patients underwent conversion

Table 2. Treatment response

	Overall (N=117)	First line chemotherapy			
		SLOG (N=48)	mFOLFIRINOX (N=21)	GOFL (N=21)	Others (N=27)
Best tumor response					
Partial response	30 (25.6%)	16 (33.3%)	6 (28.6%)	4 (19.0%)	4 (14.8%)
Stable disease	69 (59.0%)	24 (50.0%)	14 (66.7%)	14 (66.7%)	17 (63.0%)
Progressive disease	13 (11.1%)	5 (10.4%)	1 (4.8%)	3 (14.3%)	4 (14.8%)
Not evaluable	5 (4.3%)	3 (6.3%)	0 (0%)	0 (0%)	2 (7.4%)
Resected status					
R0	23 (19.7%)	15 (31.3%)	3 (14.3%)	4 (19.0%)	1 (3.7%)
R1	11 (9.4%)	5 (10.4%)	0 (0%)	4 (19.0%)	2 (7.4%)
R2	2 (1.7%)	0 (0%)	0 (0%)	1 (4.8%)	1 (3.7%)
Unresectable intraoperatively	8 (6.8%)	1 (2.1%)	5 (23.8%)	2 (9.5%)	0 (0%)
No surgical exploration	73 (62.4%)	27 (56.3%)	13 (61.9%)	10 (47.6%)	23 (85.2%)

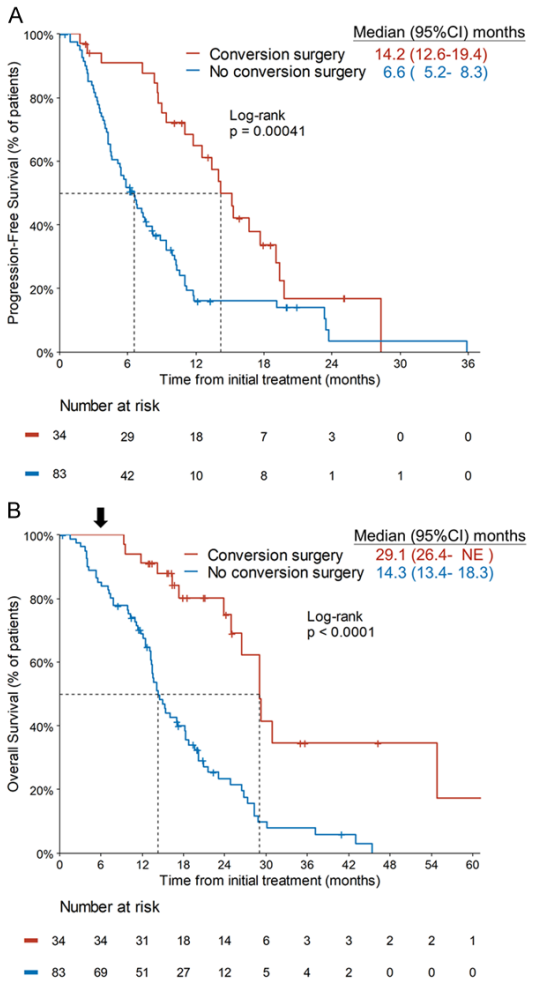

Figure 3. Survival impact of conversion surgery. A. Progression-free survival in patients with and without conversion surgery. B. Overall survival in patients with and without conversion surgery. Arrow indicated immortal time bias.

surgery after second line chemotherapy, including 2 stable disease and 1 progressive disease during first line treatment.

The survival of patients who underwent conversion surgery was significantly better than those without conversion surgery with a corresponding mPFS of 14.2 months (95% CI, 12.6-19.4) versus 6.6 months (95% CI, 5.2-8.3) and mOS of 29.1 months (95% CI, 26.4-NE) versus 14.3 months (95% CI, 13.4-18.3) months (P<0.0001) (**Figure 3A** and **3B**). To minimize possible selection bias, propensity score matching analysis with 1:1 matching and caliper of 0.1 was performed. Baseline characteristics were better balanced after propensity score matching. The survival benefit of conversion surgery remained significant after matching with a mOS of 29.0 months (95% CI, 23.8-NE) months and 17.7 months (95% CI, 14.1-28.8) in patients with or without conversion surgery (P=0.032). A multivariate Cox proportional hazard model was constructed to adjust all possible confounding factors including age, gender, tumor size, different regimen and treatment response. After adjustment, the survival benefit of conversion surgery remained significant with a hazard ratio of 0.2 (95% CI, 0.10-0.40) (**Table 3**).

Impact of consolidative CCRT

A total of 31 patients underwent consolidation CCRT after induction chemotherapy including 26 patients enrolled in the investigator-initiated trial T2212 and underwent consolidative

Table 3. Multivariate Cox proportional hazard model

Variable	HR (95% CI)	P
Age	1.00 (0.97-1.02)	0.88
Gender		
Female	Reference	-
Male	0.80 (0.49-1.29)	0.36
Tumor size	1.03 (0.90-1.19)	0.65
First line treatment		
Gemcitabine or S1 monotherapy	Reference	-
SLOG	0.82 (0.33-2.04)	0.66
mFOLFIRINOX	0.45 (0.17-1.17)	0.10
GOFL	0.66 (0.25-1.75)	0.40
Gemcitabine+S1	0.41 (0.14-1.22)	0.11
Gemcitabine+nab-paclitaxel	0.20 (0.06-0.75)	0.02
Other combination	0.79 (0.19-3.23)	0.74
Best overall response		
Partial response	Reference	-
Stable disease	1.50 (0.84-2.68)	0.17
Progression disease	5.79 (2.47-13.56)	<0.001
Not evaluable	40.11 (8.64-186.31)	<0.001
Conversion surgery		
No	Reference	-
Yes	0.20 (0.10-0.40)	<0.001

CCRT according to protocol [14]. The mOS was 18.8 months (95% CI, 15.4-24.9) months as compared to 18.2 months (95% CI, 13.7-26.4) months for patients received induction chemotherapy only (P=0.5). The conversion surgery rate was not different between patients with or without consolidative CCRT, 29.0% versus 29.1%, respectively.

Forty-four patients were enrolled in the clinical trial in the first line setting including 36 patients in T2212, 7 patients in T5217 and 1 patient in T1216 trial, all clinical trials belonging to the Taiwan Cooperative Oncology Group (TCOG) [14, 17, 19]. The mPFS and mOS for patients enrolled in the clinical trial were 8.3 months (95% CI, 6.6-11.0) and 18.3 months (95% CI, 16.1-27.3) while 8.7months (95% CI, 5.4-11.2) and 17.0 months (95% CI, 14.1-26.5) for those not enrolled in the clinical trial (**Figure 4A** and **4B**).

Pathological characteristics and adjuvant chemotherapy

The pathological characteristics of 34 patients who underwent conversion surgery were summarized in **Table 4**. Two patients achieved complete pathological remission. The median number of lymph node dissections was 20. R0 resection was achieved in 23 patients (65.7%). At data cut-off, 24 of 34 resected patients experienced tumor recurrence. The mRFS was 11.2 months (95% CI, 7.2-20.2) in patients with R0 resection while 3.8 months (95% CI, 1.2-14.8) in patients with R1 resection (**Figure 5A**). The corresponding mOS in patients with R0 resection or R1 resection were 29.2 months (95% CI, 24.9-NE) and 26.4 months (95% CI, 9.6-30.9) (**Figure 5B**). Pathological response was not reported in 2 patients. Major pathological response (tumor regression grade 0-1) was observed in 11 patients (31.4%). The mRFS and mOS was 11 months and not reached in patients with major pathological response while 10 months and 26.4 months in patients without major pathological response.

Five patients (14.7%) did not receive adjuvant chemotherapy including 3 patient's refusal and 2 early recurrence within 2 months. Both patients with early recurrence had R1 resection. Eighteen patients (52.9%) received the same regimen as induction chemotherapy used while 11 patients (32.4%) received different regimens (**Table 4**). For patients using different

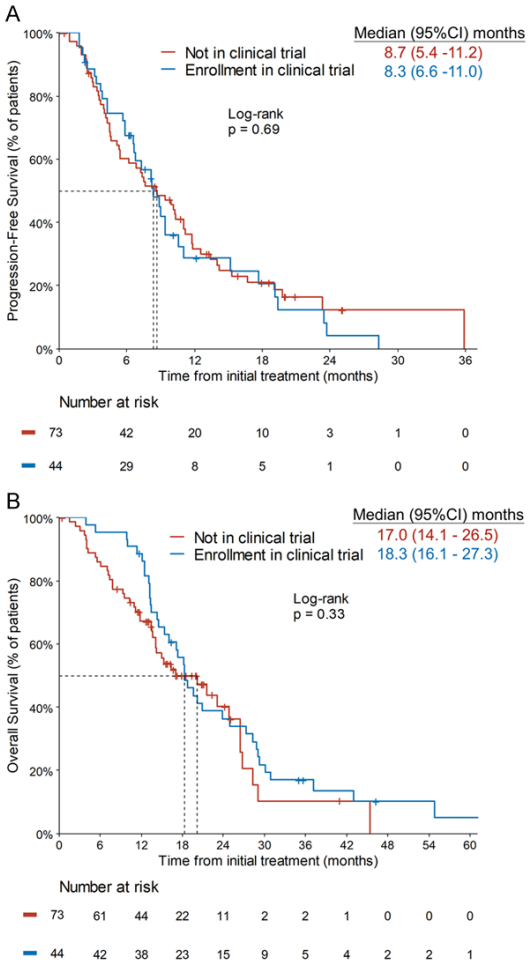

Figure 4. Survival impact of enrollment in clinical trial. A. Progression-free survival in patients who enrolled in clinical trial or not. B. Overall survival in patients who enrolled in clinical trial or not.

regimens as adjuvant chemotherapy, only gemcitabine alone, S1 alone or gemcitabine plus S1 were used (**Figure 5C**). No patient received mFOLFIRINOX as adjuvant chemotherapy. Three patients (2 clinical progression and 1 radiological progression) underwent conversion surgery after re-induction with second line chemotherapy. One patient using SLOG as first line induction chemotherapy switched to nal-IRI+5-FU/LV; another patient receiving first line mFOLFIRINOX switched to gemcitabine+S1 and the other undergoing nab-P+Gem initially then switched to nal-IRI+5-FU/LV+oxaliplatin (NALIRINOX) (**Figure 5C**).

Safey profiles

All three triplet were well-tolerated and the most common grade 3-4 adverse effects were neutropenia (18.8%-42.9%) and thrombocytopenia (4.8%-18.8%) (**Table 5**). The SLOG regimen had fewer grade 3-4 neutropenia but more grade 3-4 thrombocytopenia. No significant difference in adverse events were observed between patients who underwent conversion surgery or not.

Discussion

Our study demonstrated induction chemotherapy could achieve a mPFS of 8.6 months and a mOS of 18.3 months in patients with LAPC. In our study, 44 of 117 patients (38%) underwent surgical exploration and 34 patients (29%) who achieved complete resection had a mOS of 29.1 months. Our study unbiasedly enrolled all patients with LAPC treated in our institute. To the best of our knowledge, our study is the first report of an unbiased cohort of LAPC in Asian population.

Our study was comparable to the experience from Johns Hopkins Hospital which 116 of 461 patients (28%) underwent surgical exploration and 84 patients (20%) achieved complete resection yielding a mOS of 35.3 months [20]. Similarly, Reni et al reported a 21/151 (13.9%) resection rate in LAPC with a mOS of 30.0 months in resected patients [21]. Recently, the multi-center NEOLAP study also reported a similar result that 82 of 130 patients (63%) underwent surgical exploration and 52 patients (40%) with complete resection had a mOS of 27.5 months [22]. Notably, in the LAP-07 study, although only 18 of 442 patients (4%) underwent conversion surgery, the mOS was 30.9 months in resected patients [8].

Patients eligible for conversion surgery is no doubt a highly selected population and therefore a better survival is apparently expected. Concerning selection bias, the usefulness of conversion surgery in chemotherapy responder was questioned by the observation that, in the study from the Heidelberg group, 76 of 125 patients (60.8%) underwent conversion surgery following induction FOLFINONOX with an estimated mOS of 22.5 months while induction FOLFIRINOX yielding a mOS of 24.2 months with only 25.9% resection rate in a patient level meta-analysis [23-25]. As demonstrated in **Figure 2B**, a horizontal line from 0 to 6 months on the Kaplan-Meier curve in conversion surgery group indicated a immortal time bias

Table 4. Pathological characteristic

	Conversion surgery (N=34)
Time to surgery, months, median (range)	6.20 (2.91-13.6)
Pathological stage	
pCR	2 (5.9%)
IA	2 (5.9%)
IB	5 (14.7%)
IIA	8 (23.5%)
IIB	12 (35.3%)
III	5 (14.7%)
LN dissected, median (range)	20 (2-46)
LN positivity, %, median (range)	0 (0-33.3)
LN involvement	
N0	20 (58.8%)
N1	14 (41.2%)
Resection margin	
R0	23 (67.6%)
R1	11 (32.4%)
Tumor regression grade	
TRG 0-1	11 (32.4%)
TRG 2-3	21 (61.8%)
Not reported	2 (5.9%)
Adjuvant chemotherapy	
Same as induction chemotherapy	18 (52.9%)
Different regimen	11 (32.4%)
No adjuvant chemotherapy	5 (14.7%)

which is a common but often underestimated problem [26]. Not only immortal time bias but also other possible selection bias in our study was managed as much as possible by propensity score matching and Cox regression analysis. The benefit of conversion surgery remained significant after matching and adjusting which provided a real-world evidence to support the role of conversion surgery after induction chemotherapy. Similarly, immortal time bias was also demonstrated in the study from Johns Hopkins Hospital and the survival benefit remained significant after adjustment which justified the role of conversion surgery after induction chemotherapy. Considering ethical issues, patient and physician preference, it is almost impossible to conduct a randomized controlled trial comparing continued chemotherapy versus conversion surgery in patients whose disease did not progress after induction chemotherapy. A high-quality real-world evidence is highly demanded and our study thus filling the gap between clinical trial and clinical practice.

The selection criteria of surgical exploration after induction chemotherapy remains undetermined. The Japanese Society of Hepato-Biliary-Pancreatic Surgery suggested conversion surgery in patients who received non-surgical anticancer treatment for more than 240 days [27]. The NCCN guideline suggested surgical exploration in feasible patients who was not progressed after a 4-6 months induction chemotherapy without detailed definition [11]. The ASCO guideline suggested conversion surgery should only be considered at high-volume centers while ESMO guideline did not offer any comment regarding to this issue [10, 28]. In our study, 52.9% of resected patients did not fulfill the response criteria of RECIST 1.1 but successfully underwent conversion surgery. On the other hand, 18.1% of patients had partial response as per RESCIST but did not underwent conversion surgery which suggested radiological response alone was not an reliable indicator of conversion surgery. The survival benefit of conversion surgery remained significant after propensity score matching and

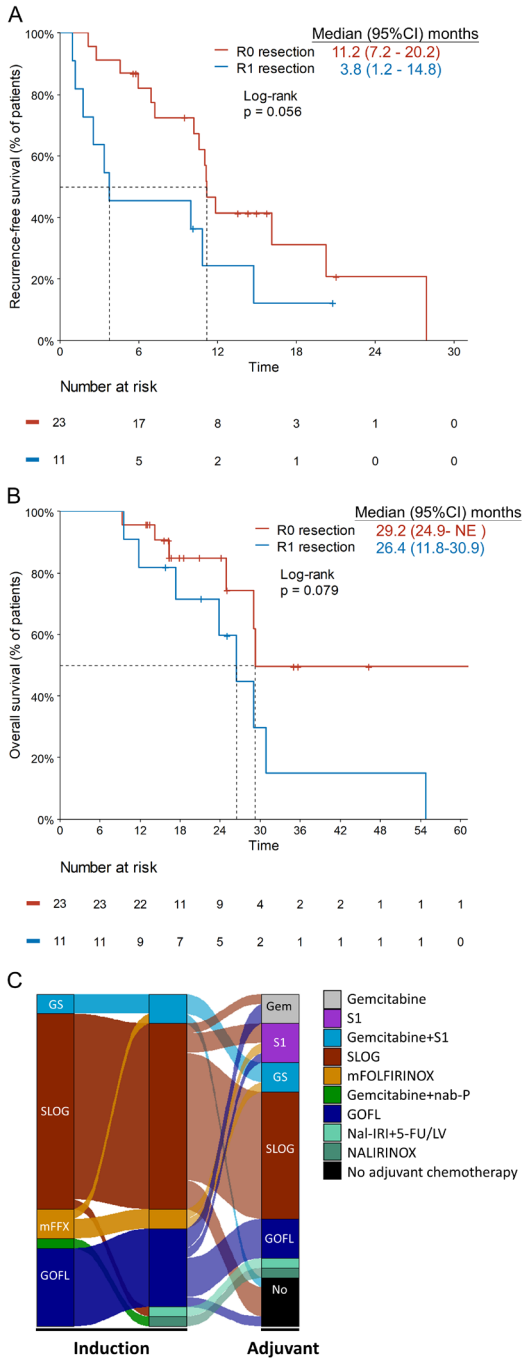

Figure 5. Outcome in resected patients. A. Recurrence-free survival in patients with R0 and R1 resection. B. Overall survival in patients with R0 and R1 resection. C. Regimen used in induction phase and adjuvant setting. Three patients successfully underwent conversion surgery after second line chemotherapy.

adjusting with Cox regression analysis which suggested a more aggressive surgical exploration strategy may be beneficial. Our experience was consistent with previous report that radiological evaluation alone is not reliable to determine resectability and a more aggressive surgical exploration strategy should be considered in all patients without progressive disease after neoadjuvant chemotherapy [20].

While induction chemotherapy with a newer combination regimen is recommended, the optimal regimen is still unclear. The GERCOR and GISCAD trial was the only phase III randomized controlled trial comparing the efficacy of combination chemotherapy versus gemcitabine monotherapy in LAPC [29]. A total of 157 and 156 patients were allocated to the gemcitabine plus oxaliplatin or gemcitabine monotherapy, respectively. The addition of oxaliplatin significantly increased ORR from 17.3% to 26.8% and mPFS increased from 3.7 months to 5.8 months. However, no significant improvement of mOS was observed (7.1 months versus 9.0 months, P=0.13). As a result, the ESMO guideline stated that gemcitabine monotherapy remained the standard of care in LAPC [28]. On the other hand, the ASCO guideline and the NCCN guideline suggested combination chemotherapy rather than monotherapy based on retrospective studies and expert experience in LAPC or experience from metastatic PDAC [10, 11, 30]. In fact, the resection rate following induction therapy in LAPC was relatively low in the era of gemcitabine monotherapy. Only 5 of 119 patients (4.2%) in the phase III FFCD/SFRO trial, 2 of 313 patients (1%) in the phase III GERCOR and GISCAD trial, 5 of 74 (6.8%) patients in the phase II SCALOP trial and 18 of 442 (4%) in the phase III LAP-07 trial underwent resection after induction therapy [7, 8, 29, 31]. By contrast, FOLFIRINOX achieved a 26% resection rate in a patient level pooled meta-analysis and the combination of nab-P+Gem demonstrated a 16% resection rate in the single arm multi-center phase II LPACT trial [25, 32]. In our study, the tumor response rate (19%-33%), the surgical exploration rate (38%-52%) and the mOS (15.4-23.0 months) were not significantly different among three triplets SLOG, mFOLFIRINOX and GOFL. Nab-P+Gem, another commonly used regimen in metastatic PDAC, yield a tumor response rate of 36/107 (33.6%), a surgical exploration rate of 20/107 (18.7%) and a mOS of 18.8 months in the single arm multi-center LAPACT trial [32]. Recently, in the randomized phase II NEOLAP trial, nab-P+Gem arm or sequential FOLFIRINOX arm yielded a similar tumor response rate (22% vs.

Table 5. Safety profile of commonly used triplet

	SLOG		mFOLFIRINOX		GOFL	
	Conversion Surgery (N=20)	No Conversion Surgery (N=28)	Conversion Surgery (N=3)	No Conversion Surgery (N=18)	Conversion Surgery (N=8)	No Conversion Surgery (N=13)
Neutropenia						
Grade 0	11 (55.0%)	12 (42.9%)	1 (33.3%)	6 (33.3%)	2 (25.0%)	4 (30.8%)
Grade 1-2	6 (30.0%)	10 (35.7%)	1 (33.3%)	4 (22.2%)	3 (37.5%)	7 (53.8%)
Grade 3-4	3 (15.0%)	6 (21.4%)	1 (33.3%)	8 (44.4%)	3 (37.5%)	2 (15.4%)
Anemia						
Grade 0	1 (5.0%)	4 (14.3%)	0 (0%)	1 (5.6%)	1 (12.5%)	2 (15.4%)
Grade 1-2	17 (85.0%)	19 (67.9%)	3 (100%)	17 (94.4%)	6 (75.0%)	10 (76.9%)
Grade 3-4	2 (10.0%)	5 (17.9%)	0 (0%)	0 (0%)	1 (12.5%)	1 (7.7%)
Thrombocytopenia						
Grade 0	6 (30.0%)	9 (32.1%)	1 (33.3%)	8 (44.4%)	0 (0%)	1 (7.7%)
Grade 1-2	11 (55.0%)	13 (46.4%)	2 (66.7%)	9 (50.0%)	7 (87.5%)	11 (84.6%)
Grade 3-4	3 (15.0%)	6 (21.4%)	0 (0%)	1 (5.6%)	1 (12.5%)	1 (7.7%)
Creatinine increased						
Grade 0	17 (85.0%)	22 (78.6%)	3 (100%)	17 (94.4%)	7 (87.5%)	12 (92.3%)
Grade 1-2	3 (15.0%)	6 (21.4%)	0 (0%)	1 (5.6%)	1 (12.5%)	1 (7.7%)
Hepatitis						
Grade 0	13 (65.0%)	15 (53.6%)	3 (100%)	15 (83.3%)	2 (25.0%)	8 (61.5%)
Grade 1-2	6 (30.0%)	13 (46.4%)	0 (0%)	2 (11.1%)	5 (62.5%)	5 (38.5%)
Grade 3-4	1 (5.0%)	0 (0%)	0 (0%)	1 (5.6%)	1 (12.5%)	0 (0%)
Hyperbilirubinemia						
Grade 0	17 (85.0%)	25 (89.3%)	3 (100%)	18 (100%)	7 (87.5%)	13 (100%)
Grade 1-2	2 (10.0%)	2 (7.1%)	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)
Grade 3-4	1 (5.0%)	1 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

17%), surgical exploration rate (62.5% vs. 63.6%) and similar mOS (18.5 months vs. 20.7 months) which suggested both regimen were reasonable to be used as induction chemotherapy [22]. However, both nab-P+Gem and FOLFIRINOX were reported with a 70.6-77.8% grade 3-4 neutropenia in Asian population which might limited the use of both regimen as neoadjuvant therapy in Asian population [13, 33]. On the other hand, both GOFL or SLOG regimen demonstrated comparable efficacy but less grade 3-4 neutropenia as compared to modified FOLFIRINOX in multicenter randomization studies [14-17]. Our single institute experience was in line with previous studies that SLOG or GOFL regimen had comparable efficacy and less neutropenia as compared to mFOLFIRINOX, and could be served as one of first line treatment option in Asian population.

Our study had some limitations. Firstly, although the SLOG regimen achieved numerically better survival, current study was a retrospective single institutional experience. The management of LAPC required a multidisciplinary team which made the practice pattern heterogenous in different hospitals. As a result, external validation in other institutes will be necessary. A prospective multicenter single arm study (NCT05048524) is ongoing to confirm the efficacy of SLOG regimen in localized PDAC. Secondly, some of the patients in our cohort participated in investigator-initiated clinical trials which made our study not a pure real-world study. But all patients treated in our institute, even those who received only one dose of chemotherapy, were identified and analyzed with an intention to treat basis which made our study a reflection of real-world practice. Besides, there was no survival difference between patients who enrolled in the clinical trial or not.

Conclusions

In this retrospective study, induction chemotherapy with either mFOLFIRINOX, GOFL or

SLOG achieved an improved resection rate and survival in patients with LAPC. Both GOFL and SLOG regimen had comparable efficacy and less neutropenia as compared to mFOLFIRINOX, and could be served as one of first line treatment option in Asian population. Radiological response was not a reliable indicator of successful conversion surgery. Patients who underwent conversion surgery had significantly better survival and thus highlighted the importance of surgical exploration in all patients who did not have progressive disease after induction chemotherapy.

Disclosure of conflict of interest

None.

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